Aryliododifluoromethylsulfides, sulfoxides and sulfones: the first optically active compounds with polyfluoroalkyliodo groups

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Aryliododifluoromethyl sulfoxides, which were transformed in aryliododifluoromethyl sulfides and sulfones, were obtained by the coupling of mercury salts of arylsulfoxydifluoromethylacetic acids with iodine.

Fluorinated alkyl iodides are among the most wide-applied reagents in organofluorine chemistry. They are used for the perfluoroalkylation of unsaturated compounds and thiols. They react with metals, sulfur, phosphorus, *etc.* Many publications are dedicated to the synthesis and study of the reactivity of fluoroalkyl iodides.^{1–4} The syntheses of polyfluoroalkyl iodides that contain different functional groups are of great interest.

In this work, we synthesised fluoroalkyl iodides that contain thio,⁵ sulfinyl and sulfonyl^{6,7} groups. Fluoroalkyl iodides with sulfinyl groups are chiral; this opens a route to optically active fluoroalkyl iodides. The presence of a difluoromethylene group at the chiral sulfur atom may allow one to monitor the optical activity and purity of the compounds by ¹⁹F NMR spectroscopy.

Earlier, we reported the synthesis of a new type of fluorocontaining sulfoxides: arylsulfinyldifluoroacetic acids.^{8,9} These acids are starting compounds for the synthesis of sulfinyldifluoromethyl iodides.



Scheme 1 Synthesis of aryliododifluoromethyl sulfoxides.

The Borodin–Hunsdiecker reaction is most widely used for the syntheses of polyfluoroalkyl iodides. In the reaction with iodine, a silver or sodium salt of a corresponding carboxylic acid is commonly used. In the case of arylsulfoxydifluoroacetic acids, the sodium salt does not give the Borodin–Hunsdiecker reaction, and the silver salt leads to a product free of fluorine. We managed to get arylsulfinyldifluoroacetic acids, which react with iodine giving arylsulfinyldifluoromethyl iodides **1a–c**.[†]

[†] *General procedures.* Boiling and melting points are uncorrected. NMR spectra were measured on a Varian VXR-300 instrument (300 MHz for ¹H, TMS as internal standard; 288 MHz for ¹⁹F, CCl₃F as internal standard).

Preparation of arylsulfinyldifluoromethyl iodides 1. Mercury oxide (0.05 mol) was added to a mixture of 0.05 mol of corresponding arylsulfoxidifluoroacetic acid in 10 ml of anhydrous dichloroethane. The mixture was heated to boiling point and stirred for 30 min until bulky precipitate of mercury salt formed. A solution of 0.05 mol of iodine in 10 ml of anhydrous dichloroethane was added to the reaction mixture. The reaction mixture was refluxed with stirring for 4 h, controlled by TLC. On completeness of the reaction it was cooled to 10 °C and filtered. The solvent was distilled off, the product was purified by column chromatography (benzene–hexane). Yields 35–75%.

1a: oil. ¹H NMR (CDCl₃) δ : 7.52–7.73 (m, 5H). ¹⁹F NMR, δ : -44.2 (d, 1F, *J* 169 Hz), -48.9 (d, 1F, *J* 169 Hz). Found (%): I, 41.76; S, 10.40. Calc. for C₇H₅IF₂OS (%): I, 42.05; S, 10.59.

1b: ¹H NMR (CDCl₃) δ : 3.97 (s, 3H), 6.53–7.72 (m, 4H). ¹9F NMR, δ : -44.8 (d, 1F, J 170 Hz), -49.1 (d, 1F, J 170 Hz). Found (%): I, 38.53; S, 9.44. Calc. for C₈H₇IF₂O₂S (%): I, 38.25; S, 9.64.

1c: oil. ¹H NMR (CDCl₃) δ : 7.55–7.71 (m, 4H). ¹⁹F NMR, δ : -44.3 (d, 1F, *J* 172 Hz), -49.0 (d, 1F, *J* 172 Hz). Found (%): I, 37.73; S, 9.51. Calc. for C₇H₄ClIF₂OS (%): I, 37.79; S, 9.52.

Arylsulfinyldifluoromethyl iodides were transformed to the corresponding sulfides and sulfones. During the reaction of arylsulfinyldifluoromethyl iodides with PCl₅ in a POCl₃ solution, the replacement of oxygen by two chlorine atoms takes place¹⁰ with the formation of corresponding arylthiodifluoromethyl iodides **2a–c**.[‡]

The reaction occurred at 15–20 °C for 30 min. At a higher temperature, arylthiodifluoromethyl chlorides are formed as by-products. Corresponding arylsulfonyldifluoromethyl iodides **3a–c** were obtained from sulfinyldifluoromethyl iodides by oxidation with *m*-chloroperbenzoic acid (MCPBA).[§]



Scheme 2 Transformation of aryliododifluoromethyl sulfoxides into corresponding sulfides and sulfones.

[‡] *Preparation of arylthiodifluoromethyl iodides* **2**. PCl_5 (0.01 mol) was added by small portions with intense stirring to a solution of 0.01 mol of arylsulfoxydifluoromethyl iodide **1** in 2 ml of $POCl_3$ at 0–5 °C. After that it was heated to 15–20 °C. The chlorine evolved vigorously. The reaction progress was controlled by TLC. At the end of the reaction, the reaction mixture was poured on ice with intense stirring. The product was extracted by CH_2Cl_2 (2×5 ml) and dried over MgSO₄. The solvent was distilled off, the product was purified by column chromatography from hexane. Yields 45–65%.

 $\begin{array}{l} \textbf{2a: oil. }^{1}\text{H NMR} \ (\text{CDCl}_3) \ \delta: 7.58 - 7.93 \ (m, 5\text{H}). \, ^{19}\text{F NMR}, \delta: -27.9 \ (s). \\ \text{Found} \ (\%): \ I, 44.68; \ S, 11.45. \ \text{Calc. for} \ C_7\text{H}_3\text{IF}_2\text{S} \ (\%): \ I, 44.40; \ S, 11.19. \\ \textbf{2b: oil. }^{1}\text{H NMR} \ (\text{CDCl}_3) \ \delta: 3.93 \ (s, 3\text{H}), 6.52 - 7.63 \ (m, 4\text{H}). \, ^{19}\text{F NMR}, \end{array}$

2b: oil. ¹H NMR (CDCl₃) δ : 3.93 (s, 3H), 6.52–7.63 (m, 4H). ¹⁹F NMR, δ : –28.3 (s). Found (%): I, 40.32; S, 10.30. Calc. for C₈H₇IF₂OS (%): I, 40.19; S, 10.13.

2c: oil. ¹H NMR (CDCl₃) δ : 7.55–7.71 (m, 4H). ¹⁹F NMR, δ : –28.7 (s). Found (%): I, 40.07; S, 10.21. Calc. for C₇H₄CIIF₂S (%): I, 39.69; S, 10.02. [§] *Preparation of arylsulfonyldifluoromethyl iodides* **3a–c**. At room temperature, 0.03 mol of MCPBA was added to a solution of 0.02 mol of arylsulfoxydifluoromethyl iodide **1** in 5 ml of anhydrous CH₂Cl₂. The reaction mixture was stirred at room temperature until iodide **1** disappeared according to TLC data. At the end of the reaction, the mixture was cooled to –10 °C and the precipitated *m*-chlorobenzoic acid was filtered off. The solvent was distilled off. The product was purified by column chromatography (ethyl acetate–hexane). Yields 70–85%.

3a: mp 66–68 °C. ¹H NMR ($CDCl_3$) δ : 7.61–8.01 (m, 5H). ¹⁹F NMR, δ : –52.5 (s). Found (%): I, 40.11; S, 10.32. Calc. for $C_7H_5IF_2O_2S$ (%): I, 39.94; S, 10.08.

3b: mp 93–95 °C. ¹H NMR (CDCl₃) δ : 3.92 (s, 3H), 7.06–7.92 (m, 4H). ¹⁹F NMR, δ : –54.7 (s). Found (%): I, 36.32; S, 9.30. Calc. for C₈H₇IF₂O₃S (%): I, 36.49; S, 9.19.

3c: mp 104–105 °C. ¹H NMR [(CD₃)₂CO] δ : 7.86–8.09 (m, 4H). ¹⁹F NMR, δ : –55.5 (s). Found (%): I, 35.92; S, 9.12. Calc. for C₇H₄ClIF₂O₂S (%): I, 36.07; S, 9.09. The obtained difluoromethyl iodides were introduced into reactions with aldehydes and unsaturated compounds, and reduction reaction.

Thus, *p*-chlorophenylsulfinyldifluoromethyl iodide reacts with *p*-methylbenzaldehyde in the presence of tetrakis(diethylamino)-ethylene (TDAE) and gives corresponding secondary alcohol **4** in 60% yield as a diastereomer mixture. Likewise, the *p*-chlorophenylsulfonyldifluoromethyl iodide reacts with *p*-methylbenz-aldehyde.[¶]



Scheme 3 Reaction of 1c and 3c with *p*-methylbenzaldehyde.

p-Chlorophenylsulfinyldifluoromethyl iodide reacts with zinc in dimethylformamide (DMF) at room temperature to form corresponding difluoromethylsulfoxide **6** in high yield.^{††}



Scheme 4 Reaction of 1c with zinc.

An attempt to add sulfinyldifluoromethyl iodide to the double bond of styrene under UV irradiation of the reaction mixture yielded a hard-to-separate mixture of products. The use of azoisobutyronitrile (AIBN) as a catalyst did not cause the addition of difluoromethyl iodides to double bonds, and benzoyl peroxide oxidised the sulfinyldifluoromethyl group to sulfone.

Earlier, we have elaborated the synthesis of the first optically active fluorocontaining sulfoxides with fluorinated groups bounded directly to the centre of optical activity, namely, sulfur.⁸

[¶] The synthesis of p-chlorophenylsulfinyl- and sulfonyldifluoromethylp-tolylcarbinols **4** and **5**. Iodide **1c** or **3c** (0.02 mol) was added to 1 ml of *p*-methylbenzaldehyde, the mixture was cooled to -15 °C under argon, after that 0.02 mol of TDAE was added with intense stirring. The reaction mixture was kept at this temperature for 1.5 h. Then, the temperature was slowly raised to room temperature, the mixture was stirred until the orangebrown colour disappeared. After the end of the reaction, water was added, the mixture was acidified to pH 4–5. The product was extracted by 3×5 ml of CH₂Cl₂. The combined organic phase was washed with ice-cold water and dried over MgSO₄. The solvent was distilled off, the product was purified by column chromatography (ethyl acetate–hexane).

4: ¹H NMR [(CD₃)₂CO] δ : 2.66 (d, 3H), 4.69 (br. s, 1H), 5.49–5.73 (m, 1H), 7.47–7.97 (m, 8H). ¹⁹F NMR, δ : -111.2 (ddd, J_{FF} 217 Hz, J_{FH} 14 Hz), -111.5 (d, J_{FF} 222 Hz), -117.5 (ddd, J_{FF} 222 Hz, J_{FH} 23 Hz), -118.9 (ddd, J_{FF} 217 Hz, J_{FH} 14 Hz). MS, m/z (RI): 330 (4.5), 162 (37), 160 (100), 121 (30), 112 (27).

5: ¹H NMR [(CD₃)₂CO] δ : 2.43 (s, 3H), 4.89 (br. s, 1H), 5.51 (dd, 1H, J_1 20 Hz, J_2 3 Hz), 7.17–7.93 (m, 8H). ¹⁹F NMR, δ : –104.5 (d, $J_{\rm FF}$ 234 Hz), –118.2 (dd, $J_{\rm FF}$ 234 Hz, $J_{\rm FH}$ 20 Hz). MS, m/z (RI): 175 (0.2), 170 (2), 121 (100), 94 (11).

^{††} *Preparation of* p-*chlorophenyldifluoromethyl sulfoxide* **6**. Zinc dust (0.02 mol) was added to a solution of iodide **1c** in 2 ml of DMF and stirred at room temperature until the iodide disappeared, according to TLC; then, the mixture was poured into water. The product was extracted by 3×5 ml of diethyl ether. The combined organic phase was washed with 2×5 ml of cold water and dried over MgSO₄. The solvent was distilled off, the product was purified by column chromatography (benzene-hexane); mp 74–75 °C. ¹H NMR (CDCl₃) δ : 5.6 (t, 1H, *J* 54 Hz), 7.54–7.63 (m, 4H). ¹⁹F NMR, δ : –119.7 (dd, 2F, *J* 252 Hz), –121.5 (dd, 2F, *J* 252 Hz). Found (%): C, 40.33; H, 2.43; S, 15.30. Calc. for C₇H₅ClF₂OS (%): C, 39.91; H, 2.38; S, 15.23.

We established that it is possible to obtain the corresponding optically active sulfinyldifluoromethyl iodides and difluoromethyl sulfoxides from optically active sulfinyldifluoroacetic acids.

Optically active (+)-*p*-chlorophenylsulfinyldifluoroacetic acid (98% ee) was taken as a model compound. The optically active difluoromethyl iodide containing the sulfinyl group was obtained from this acid according to the above method in 75% yield.^{‡‡}



 $[\alpha]_{D}^{20}$ +171.4° (c 0.01, CH₂Cl₂), 98% ee

Scheme 5 Synthesis of optically active *p*-chlorophenylsulfinyldifluoromethyl iodide.

The optically active *p*-chlorophenyldifluoromethyl sulfoxide was synthesised in a reaction of (+)-*p*-chlorophenylsulfinyl-difluoromethyl iodide with zinc in DMF.^{§§}



 $[\alpha]_{\rm D}^{20}$ +227.8° (c 0.01, CH₂Cl₂), 98% ee

Scheme 6 Synthesis of optically active *p*-chlorophenyldifluoromethyl sulfoxide.

The enantiomer purity was defined using ¹⁹F NMR spectroscopy in the presence of a chiral shift reagent, (+)-phenyl*tert*-butylthiophosphonic acid.¹¹

Thus, we found a new method for the synthesis of compounds with the difluoromethyliodide group directly connected to sulfide or sulfonyl groups. Sulfoxides and their optically active forms with difluoroiodomethyl and difluoromethyl groups bound to sulfur were synthesised for the first time.

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^{‡‡} *Preparation of optically active* p-*chlorophenylsulfinyldifluoromethyl iodide* **7**. Mercury oxide (0.05 mol) was added to a solution of 0.05 mol of optically active *p*-chlorophenylsulfoxydifluoracetic acid in 10 ml of anhydrous dichloroethane. The mixture was heated to the boiling point and stirred for 30 min until the precipitate of mercury salt formed. Then, the solution of 0.05 mol of iodine in 10 ml of anhydrous dichloroethane was added dropwise to the reaction mixture. The mixture was refluxed with stirring for 4 h. The end of the reaction was controlled by TLC. Then, the reaction mixture was cooled down to 10 °C and filtered. The solvent was distilled off; the product was purified by column chromatography (benzene–hexane); oil. ¹H NMR (CDCl₃) δ : 7.54–7.69 (m, 4H). ¹⁹F NMR, δ : –44.4 (d, 2F, *J* 172 Hz), –49.0 (d, 2F, *J* 172 Hz). Found (%): I, 37.54; S, 9.23. Calc. for C₇H₄CIIF₂OS (%): I, 37.79; S, 9.52.

^{§§} *Preparation of optically active* p-*chlorophenylfluoromethyl sulfoxide* **8**. Zinc dust (0.02 mol) was added to a solution of iodide **7** in 2 ml of DMF, the mixture was stirred at room temperature until iodide **7** disappeared according to TLC data. After the end of the reaction, the mixture was poured into water. The product was extracted with 3×5 ml of diethyl ether. The combined organic phase was washed with 2×5 ml of cold water and dried over MgSO₄. The solvent was distilled off; the product was purified by column chromatography (benzene–hexane); mp 91–92 °C. ¹H NMR (CDCl₃) δ : 6.0 (t, 1H, *J* 55 Hz), 7.57–7.68 (m, 4H). ¹⁹F NMR, δ : –119.0 (dd, 2F, *J* 252 Hz), –120.6 (dd, 2F, *J* 252 Hz). Found (%): C, 39.71; H, 2.55; S, 15.52. Calc. for C₇H₅CIF₂OS (%): C, 39.91; H, 2.38; S, 15.23.

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